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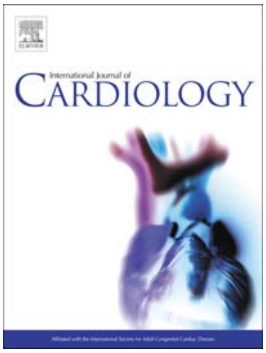

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Dabigatran in clinical practice: contemporary overview of the evidence

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Key words:

dabigatran, atrial fibrillation, systemic embolism, venous thromboembolism

Abstract

Oral anticoagulation is the cornerstone of stroke prevention in non-valvular atrial fibrillation (AF) and management of venous thromboembolism (VTE), resulting in a reduction in thrombotic complications and mortality. Benefit of vitamin K antagonists (VKAs) in such patients have been unambiguously confirmed, but VKA use is complicated by need for regular monitoring of the international normalized ratio and multiple drug and food interactions.

Dabigatran is an oral direct thrombin inhibitor that can be used with fixed doses, without the need for routine anticoagulation laboratory monitoring and the advantage of few drug or diet interactions. Dabigatran is effective for stroke and systemic thromboembolism in AF and for the prophylaxis and treatment of VTE. The drug has a good safety profile and consistently shows a reduction in intracranial haemorrhage risk compared to warfarin. A specific reversal agent for dabigatran has been approved by FDA and EU. This review provides a summary of publications assessing clinical utility of dabigatran for different indications.

Introduction

Introduction of oral anticoagulation as a preferable choice for stroke prevention in non-valvular atrial fibrillation (AF) has dramatically changed outlook in this common condition.[1] In the Stroke Prevention in Atrial Fibrillation Study (SPAF) randomized, double blind trial warfarin reduced the risk of ischemic stroke and systemic embolism by two thirds compared to placebo in patients deemed eligible for warfarin treatment.[2] The meta-analysis of the clinical trials on the vitamin K antagonists (VKA) compared to placebo has demonstrated a 64% relative risk reduction in stroke or systemic embolism and rates of all-cause mortality were 26% lower in the warfarin group.[3] There was also a 39% relative risk reduction in all strokes with VKA compared to aspirin.[3] Consequently net benefits of VKA in AF have been unambiguously confirmed and these agents became the standard for SPAF.[4, 5]

Warfarin and other VKAs have multiple pharmacokinetic and pharmacodynamics limitations including multiple food and drug interactions and need for meticulous laboratory monitoring. These limitations together with fear of bleeding complications contributed to large-scale underutilization of VKAs, particularly in older people.[6] In fact, age of more than 75 years was considered a criterion for warfarin ineligibility in the SPAF trial aiming to avoid a population with perceived high risk of hemorrhage.[2] Limitations of the VKA based oral anticoagulant (OAC) prompted development of specific inhibitors of the key components of the coagulation cascade preferably acting independently of cofactors. Thrombin has become a natural anticoagulation target of choice being the end-cascade coagulation factor for both

intrinsic and extrinsic coagulation pathways.[7]

Dabigatran etexilate (Boehringer Ingelheim) is a direct, reversible non-peptide inhibitor of both free and clot-bound thrombin (Table 1).[8] Dabigatran etexilate is a prodrug, which differs from dabigatran by an ethyl group at the carboxylic acid and a hexyloxycarbonyl side chain at the amidine, which allows better (approximately 6.5%) bioavailability on oral intake.[9, 10] The formation of dabigatran occurs by esterase-catalyzed hydrolysis in the plasma and liver. After oral intake the plasma levels of dabigatran peak within 1-2 hours. Upon regular use dabigatran has a half-life of 14-17 hours, and is used twice daily to maintain plasma concentrations and anticoagulant properties.[11-13] About 80% of dabigatran is excreted unchanged by the kidneys and 20% of the drug undergoes biliary conjugation and excretion.[13] As a result renal dysfunction delays dabigatran elimination and it is contraindicated in patients with severe renal failure. Dabigatran has low propensity to drug-drug interactions as its metabolism does not involve cytochrome P450 enzymes and it has low plasma protein binding of only 35%.[11, 14, 15] No dabigatran dose modification is needed for concomitant use with amiodarone and quinidine. In contrast to ximelagatran, dabigatran does not lead to hepatotoxicity. Dabigatran etexilate has no known interactions with food.[16]

A few drug-drug interactions still need to be considered when dabigatran is prescribed. The absorption of dabigatran etexilate in upper gastrointestinal system is affected by acidity of the content. Tartaric acid-containing capsules are used to optimize absorption of the drug and only intact capsules must be used.[17]

Dabigatran etexilate is a substrate of P-glycoprotein and the drug's concentration may vary when it is used simultaneously with potent P-glycoprotein inhibitors or inducers. For example, verapamil, a P-glycoprotein inhibitor may increase plasma concentrations of dabigatran, and dronedarone, systemic ketoconazole, cyclosporine and itraconazole are contraindicated in the European Union (EU) summary of the product characteristics. [18] Other examples of potent P-glycoprotein inhibitors are other azole-based antimycotics, various immunosuppressants, and human immunodeficiency virus protease inhibitors—their combination with dabigatran should be used with caution. Dabigatran should not be used with potent P-glycoprotein inducers such as rifampicin.

Stroke prevention in atrial fibrillation

The efficacy and safety of dabigatran for the prevention of stroke and systemic embolism in patients with non-valvular AF was assessed in the controlled, non-inferiority Randomized Evaluation of Long-term anticoagulant therapy (RE-LY) trial.[19] In this trial 18113 AF patients from 44 countries were randomized to receive 110 mg dabigatran twice daily (bid), 150 mg dabigatran bid (the two dabigatran doses were blinded) or open-labeled warfarin (dose adjusted for target international normalized ratio [INR] 2-3). The principle inclusion criteria were documented AF with one of the following: previous stroke or transient ischemic attack, a left ventricular ejection fraction ≤40%, heart failure symptoms compatible with New York Heart Association (NYHA) class II or higher within 6 months before screening, and an age of ≥75 years or a combination of age of 65-74 years with diabetes mellitus, hypertension, or coronary artery disease. The key exclusion criteria were severe

cardiac valve disease, recent stroke, increased bleeding risk, creatinine clearance <30 ml/min, active liver disease, and pregnancy. The median follow up was 2-years and all analyses were based on the intention-to-treat principle.

The primary outcome measure of stroke (including hemorrhagic stroke) and systemic embolism was significantly reduced with 150 mg bid dabigatran dose (relative risk 0.65; p <0.001), which paralleled reduction in hemorrhagic stroke from 0.38% per year in the warfarin group to 0.10% per year in the dabigatran 150 mg bid group (p <0.001).[20] No difference in the major bleeding risk was evident with this dose. The lower, 110 mg bid dose was associated with stroke risks similar to those on warfarin, but there were significantly less major bleeding events (20% relative risk reduction, p=0.003). The mortality rate was 3.75% with 110 mg of dabigatran and with 150 mg of dabigatran was 3.64% as compared with 4.13% in the warfarin group (p=0.13 for 110 mg dose and p=0.051 for 150 mg dose).[19] The favorable effects of dabigatran were evident despite well maintained time in therapeutic range in the warfarin group (i.e., mean of 64%).

Overall dabigatran was well tolerated with no evidence of liver dysfunction. However dyspepsia was about twice more common with both dabigatran doses compared to warfarin. A numerical but non-significant increase in myocardial infarction incidence was observed in the dabigatran groups (0.8%) compared to warfarin treated patients (0.6%), with 110 mg dabigatran dose (p=0.09) and with 150 mg dose (p=0.12). [21] However, treatment with 150 mg bid dabigatran dose showed significant reduction in vascular death compared to warfarin (relative risk 0.85, 95% confidence interval [CI] 0.72-0.99, p=0.021) with similar numerical trend seen for the 110 bid dose.

RELY-ABLE

Upon completion of the RE-LY trial, 48% of its participants receiving dabigatran were enrolled into the follow-up Long-term Multicenter Extension of Dabigatran Treatment in Patients with Atrial Fibrillation (RELY-ABLE) trial. After a median follow-up of 2.3 years there was no significant difference between the two dabigatran doses in rates of stroke or systemic embolism, death and hemorrhagic stroke. However the annual rates of major hemorrhage were higher with dabigatran 150 mg than 110 mg (3.74% vs 2.99%, hazard ratio [HR] 1.26, 95% CI 1.04-1.53).[22]

EU label analysis

Dabigatran has been approved by all major regulatory bodies, such US Food and Drug Administration (FDA) and the European Medicines Evaluation Agency (EMEA) for the prevention of stroke and systemic embolism in patients with non-valvular AF. However, although the recommended treatment regime aimed to resemble the RE-LY trial protocol it cannot be considered equivalent to the trial protocol, with the observational studies lacking randomization by their nature. The EU label recommends the use of 150 mg bid dabigatran dose in patients with AF who are less 80 years old and do not have an increased risk for bleeding (e.g., HAS-BLED score <3) and not receiving verapamil. All other AF patients eligible for oral anticoagulation are recommended to receive 110 mg bid dose. A post-hoc analysis of over 12000 participants of the RE-LY trial showed that when prescribed based on the EU recommendations dabigatran significantly reduced rates of stroke and systemic embolism (HR 0.74, 95% CI 0.60-0.91), hemorrhagic stroke (HR 0.22, 95% CI 95% CI 0.11-0.44), death (HR 0.86, 95% CI 0.75̃0.98), and vascular death (HR 0.80, 95%

CI 0.68-0.95).[23] Also, dabigatran showed excellent safety profile with lower risk of major bleedings (HR 0.85, 95% CI 0.73-0.98), life-threatening bleedings (HR 0.72, 95% CI 0.58-0.91), intracranial hemorrhage (HR 0.28, 95% CI 0.17-0.45), and any bleeding (HR 0.86, 95% CI 0.81-0.92). The analysis strongly suggests that when used in accordance with the EU label dabigatran has superior efficacy and safety compared to warfarin.

Renal function

Renal impairment increases the risk of stroke and bleeding in AF patients. As dabigatran is largely eliminated by renal excretion severe kidney dysfunction may increase the drug's plasma concentrations and most regulatory authorities do not recommend dabigatran in people with creatinine clearance <30 ml/min. The ESC guidelines on management of AF recommend annual assessment of renal function in individuals with baseline creatinine clearance 50–79 ml/min with more frequent assessment (2–3 times per year) in those with creatinine clearance 30–49 ml/min.[4, 5] If the creatinine clearance falls below 30 ml/min warfarin should be started instead of dabigatran. The approach is also applicable when dabigatran is used for other indications, for example VTE. A different approach is used in the US where FDA approved a lower 75 mg bid dose of dabigatran in patients with creatinine clearance 15-30 ml/min. This approach is based on pharmacokinetic modelling and has not been tested in a randomised clinical trial. In the RE-LY trial impairment of renal function was associated with higher rates of stroke and systemic embolism, major bleeding, and all-cause mortality (Figures 1-4) in all treatment arms. However, the efficacy of the both doses of dabigatran remained consistent through out the whole ranges of renal function accepted for participation in the trial.[24]

Elderly patients

Older patients with AF are less likely to receive oral anticoagulation despite evidence that benefits of oral anticoagulation outweigh any age-related increase in risk of bleeding. Simplicity of dabigatran administration brings clear benefits for management of older people and both the RE-LY and RELY-ABLE trials had no upper age restrictions. There was a significant treatment-by-age interaction regarding the risk of bleeding in the RE-LY trial.[25] Compared to warfarin, in patients younger than 75 years dabigatran was associated with almost 40% lower relative risk of major bleeding with the 110 mg bid dose and 30% lower relative risk of the major bleeding with the 150 mg bid dose ($p<0.001$ for both). In subjects aged 75 years or older the 110 mg dose was related to a similar risk of major bleeding to warfarin whilst the 150 mg dose showed a trend towards higher risk of major bleeds (5.10% vs. 4.37% with warfarin, $p=0.07$). The interactions were observed for extracranial but not intracranial bleeding events.

CHA_2DS_2-VASc score

In the RE-LY trial, higher $CHADS_2$ scores in AF patients were associated with increased risks for death, stroke or systemic embolism, bleeding in both the warfarin and dabigatran groups.[26] The clinical benefits of dabigatran established in the trial were consistent throughout the whole range of the $CHADS_2$ scores tested. A modeling analysis based on the EuroHeart Survey on AF and extrapolation of outcomes of the RE-LY trial suggested that utilization of dabigatran instead of warfarin in the European population with AF and CHA_2DS_2-VASc score ≥ 2 would annually prevent 43,235 deaths and major cardiovascular events with the 150 mg bid dose and 27,272

of such events with the 110 mg bid dose.[27]

Primary thromboembolism prevention in venous thromboembolism

VTE, that includes deep vein thrombosis (DVT) and pulmonary embolism (PE) is a significant healthcare problem associated with substantial morbidity and mortality.[28-30] A large study reported 11% 30-day and 23% 1-year case mortality in VTE.[31] Unprovoked VTE has a strong propensity for recurrence, which occurs in 1 in 10 patients within 1 year and in every third patient within 3 years.[32] VTE is associated with high healthcare costs to cover high expenses of hospitalization, professional costs, and outpatient procedures.[33]

The effectiveness and safety of dabigatran for primary venous thromboembolism (VTE) prevention in patients after major joint surgery, was established in randomized, double-blind, placebo-controlled trials (Table 2). In the RE-MODEL trial dabigatran 150 mg once daily or 220 mg once daily, starting with a half-dose 1–4 hours after total knee replacement was compared to enoxaparin 40 mg once daily starting the evening before surgery with the treatment continued for 6-10 days.[34] Both dabigatran doses were non-inferior to enoxaparin for prevention of the primary efficacy outcome of a composite of total VTE and mortality during the treatment (occurred in 37.7% of participants in the enoxaparin group, 36.4% of the 220 mg dabigatran group and 40.5% of the 150 mg dabigatran group). There was no difference in incidence of major hemorrhage between the three groups (1.3%, 1.5% and 1.3%, respectively).

In the RE-NOVATE trial dabigatran was compared with warfarin in patients

undergoing total hip replacement with treatment continued for 28–35 days.[35] Both 150 mg and 220 mg dabigatran doses were not inferior to warfarin, for prevention of VTE and all-cause mortality (6.7% in the enoxaparin group, 6.0% in the dabigatran 220 mg group and 8.6% in the 150 mg group) with no difference seen in major bleeding rates. In the phase III RE-NOVATE II trial of thromboprophylaxis for total hip replacement the primary efficacy outcome of total VTE or all-cause death was recorded in 7.7% of the dabigatran group versus 8.8% of the enoxaparin, confirming non-inferiority of dabigatran.[36]

The success of dabigatran in VTE prevention in major joint surgery was not repeated in the double-blind, randomized RE-MOBILIZE trial when the drug was tested against the North American enoxaparin regimen (30 mg bid instead of 40 mg once daily).[37] In this trial both dabigatran doses had lower efficacy compared to enoxaparin (VTE rates of 31% for 220 mg dabigatran, 34% for 150 mg dabigatran vs. 25% for enoxaparin). Major bleeding rates were similar in the three groups.

Management of venous thromboembolism

Oral and parenteral anticoagulation has been widely used to prevent VTE recurrence.[38] The commonly used treatments included heparin-based anticoagulants, such as unfractionated heparin and low-molecular-weight heparins, fondaparinux, and VKAs. Dabigatran brings significant advantages compared to those treatments being administered orally with predictable anticoagulation response and no need for laboratory monitoring of anticoagulation. Costs of dabigatran can be small compared to overall costs of management of DVT and its complications, if hospital

admissions are required.

RE-COVER I and RE-COVER II

In the double-blind, placebo-controlled noninferiority RE-COVER trial 2539 patients with acute VTE initially treated by parenteral anticoagulation (typically by intravenous heparin or subcutaneous low molecular weight heparin for a median of 9 days were randomized for 6 month treatment with oral dabigatran 150 mg bid or warfarin (INR 2.0-3.0).[39] The primary end point was a combination of symptomatic VTE or death associated with VTE within 6 months from randomization (Table 3).

The study results underwent a modified intention-to-treat analysis with patients who did not receive any study drug being excluded. In the warfarin group the INR was within the therapeutic range 60% of the time. Recurrent VTE occurred in 2.4% of patients treated with dabigatran and 2.1% of patients receiving warfarin (HR 1.10, 95% CI 0.65-1.84, $p<0.001$ for the non-inferiority test). Major bleeding occurred in 1.6% of patients receiving dabigatran and 1.9% of those on warfarin (HR 0.82, 95% CI 0.45-1.48). Any bleeding was significantly less common in the dabigatran group (16.1%) than in the warfarin group (21.9%, HR 0.71, 95% CI 0.59-0.85). There was no significant difference in rates of deaths, acute coronary syndromes or increase in liver enzymes between the treatment groups. Treatment discontinuation rates were 9.0% with dabigatran and in 6.8% with warfarin.[39] Results of the RE-COVER trial were consequently confirmed by the RE-COVER II study, which had a similar design and recruited 2589 patients.[40] Pooled analysis of the RE-COVER and RE-COVER II studies confirmed non-inferiority of dabigatran for prevention of VTE recurrence (HR 1.09, 95% CI 0.76-1.57), for risk of major bleeding (HR 0.73, 95% CI 0.48-

1.11). Analysis of the double-dummy phase of the trial, which included patients who actually received dabigatran showed significantly lower rates of major bleeding in the dabigatran group (HR 0.60, 95% CI 0.36–0.99). The analysis also showed reduction in risk for any bleeding in patients treated by dabigatran (HR 0.70, 95% CI 0.61-0.79 for the study overall and HR 0.67, 95% CI 0.59–0.77 for the double dummy phase).[40] Although the frequency of any gastrointestinal bleeds in the RE-COVER program was numerically higher with dabigatran than with warfarin, dabigatran was associated with lower rate of major gastrointestinal bleeds.[41] In the dabigatran group no increase in bleeding risk was observed in patients who were treated with nonsteroidal anti-inflammatory drugs with a half-life <12 hours or low-dose aspirin.[42]

Similarly to the AF RE-LY trial, patients with creatinine clearance <30 ml per minute were excluded from the RE-COVER and RE-COVER II studies. Given the predominantly renal route of dabigatran elimination a prespecified subgroup analysis of pooled data from RE-COVER and RE-COVER II was performed to establish the efficacy and safety of dabigatran in relation to renal function. The analysis did not find any significant treatment interaction by renal function. Dabigatran efficacy was preserved and superiority regarding any bleeding events maintained throughout the whole range of renal function eligible for inclusion into the study.[43] Dabigatran was similarly effective to warfarin across all age groups.[44, 45] Although rates of bleeding events were higher in older patients overall bleeding was less frequent in those receiving dabigatran compared to patients treated with warfarin irrespectively of age. These studies indicate no need for dabigatran dose adjustment of in patients with mild or moderate kidney dysfunction or in older subjects. However the European

Medical Agency has still advised that the lower dose of 110 mg bid should be used in patients aged 80 and above.[18]

In acute VTE management, dabigatran is started after an initial period of parenteral anticoagulation (e.g., 5 days of low molecular weight heparin in the UK or 5-10 days of heparin or low molecular weight heparin in the US). This differs from the approach used in trials of apixaban (AMPLIFY trial) and rivaroxaban (EINSTEIN-DVT study), which can be started from the disease onset.[46, 47] There is no direct comparison data on whether any one of the agents offer clinical superiority over another and all three agents are licensed for acute DVT.

The efficacy of dabigatran is similar in patients with or without active cancer.[48, 49] Patients with cancer were more prone to bleeding overall, but treatment with dabigatran was associated with fewer major bleeding (HR 0.60, 95% CI 0.36-0.99) and overall bleeding (HR 0.56, 95% CI 0.45-0.71). In the RE-COVER program there was a significantly higher frequency of recurrent VTE or VTE-related mortality among patients who had active cancer, but the efficacy of dabigatran versus warfarin was similar irrespective of cancer status.[48, 49] In the pooled analysis of the program the risk of recurrence was similar in patients who presented initially with PE or DVT and the treatment efficacy of dabigatran was not affected by the presence of thrombophilia.[50, 51]

RE-MEDY and RE-SONATE

Whilst the RE-COVER program tested efficacy and safety of dabigatran during a 6-month period of treatment, many VTE patients, particularly those with evidence of

thrombophilia or history of recurrent thrombosis require more prolonged anticoagulation.[52] The RE-COVER program was extended to establish utility of dabigatran for prolonged use in VTE in comparison to either warfarin (active control, the RE-MEDY study, n=2856) or placebo (the RE-SONATE trial, n=1343). These two randomized, double-blinded trials enrolled patients who had already completed at least 3 months of treatment for VTE.

The definition of VTE and studies' outcomes were generally similar to those in the RE-COVER program and its participants consequently contributed to almost 80% patients of the RE-MEDY study and 4.0% of subjects of the RE-SONATE study. Unexplained death was additionally included as part of the primary efficacy outcome in the RE-SONATE. Also, the trial excluded patients who received thrombolytic therapy within 14 days prior to the recruitment, had malignancy or inferior vena cava filters implanted. The median treatment duration was approximately 16 months in the RE-MEDY trial and 4.5 months in the RE-SONATE trial. Modified intention-to-treat analysis was followed similar to the RE-COVER study. Bleeding events were included into the analysis if occurred during the period between the first dose of the study drug and 3 days after administration of the last dose.

In the RE-MEDY study, recurrent VTE occurred in 1.8% of participant of the dabigatran group and 1.3% of patients in the warfarin group (HR 1.44, 95% CI 0.78-2.64; p=0.01 for non-inferiority). Major bleeding complications occurred in 0.9% of patients treated by dabigatran and 1.8% of those receiving warfarin (HR 0.52, 95% CI 0.27-1.02). Any clinically relevant bleedings were less frequent with dabigatran (HR 0.54, 95% CI 0.41-0.71). Acute coronary syndromes were recorded slightly more

frequently in the dabigatran group than in the warfarin group (0.9% vs. 0.2%, respectively, p=0.02).[53] However, this was at least partly due to the fact that more patients in the dabigatran group had coronary artery disease than in the warfarin group (8.4% and 6.1%, respectively). In the RE-MEDY trial 18% of participants had features of thrombophilia with Factor V Leiden thrombophilia being the most common type.[54] Treatment efficacy of dabigatran as compared to warfarin was not significantly affected by the presence of thrombophilia.

In the assessment based on the RE-MEDY trial criteria the net clinical benefit for a cumulative end-point of nonfatal recurrent VTE, nonfatal myocardial infarction, nonfatal stroke, nonfatal systemic embolism, all-cause death, and major bleeding events was similar between dabigatran and warfarin (HR 1.05, 95% CI 0.75-1.46). For the broader outcome that included any clinically relevant bleeding events the net clinical benefits favored dabigatran over warfarin (HR 0.73, 95% CI 0.59-0.91). Stratification of the net clinical benefit by the time in the therapeutic range in warfarin group confirmed the benefits of dabigatran treatment over warfarin despite good INR control.[55]

In the RE-SONATE study, recurrent VTE occurred more than 10-fold less frequently in the dabigatran group than in the placebo group (0.4% vs. 5.6%, respectively, HR 0.08; 95% CI 0.02-0.25; p<0.001). Major bleeding was extremely rare (in 2 patients in the dabigatran group and none in the placebo group). Any clinically relevant bleeding was more frequent in the dabigatran group (5.3% vs. 1.5%, respectively, HR 2.92; 95% CI 1.52-5.60).[53] During 1 year of extended follow-up the primary efficacy outcome events occurred 55% more frequently in the placebo than in the

dabigatran group (10.7% vs. 6.9%, respectively, p<0.05). Overall, the trial data confirm that dabigatran is as effective as warfarin and superior to placebo for extended use in VTE with a lower risk of major or clinically relevant bleedings compared to warfarin but with a higher risk compared placebo.[56] Dabigatran was generally well tolerated with no difference in the rate of drug discontinuation during its extended use compared to both warfarin and placebo.

Bleeding

Bleeding can be a serious complication of any OAC treatment and fear of bleeding is the most common reason for OAC underutilization. As discussed above dabigatran has shown favorable bleeding risk profile especially the 110 bid regimen.[19] Intracranial hemorrhage accounts for approximately 90% of deaths from warfarin-related bleeding and administration of either dabigatran dose significantly reduce the risk of hemorrhagic stroke.[19, 57, 58]

A review of major bleeding events in five phase III trials of dabigatran,[19, 39, 53, 59] which included 27,419 patients showed that subjects with major bleeds on dabigatran were older, had worse renal function and were more likely to be taking aspirin or non-steroid anti-inflammatory agents.[60] In this analysis the 30-day mortality related to major bleedings tended to be lower with dabigatran than with warfarin (9.1% vs. 13.0%; pooled odds ratio 0.68; 95% CI 0.46-1.01; p=0.057). Patients who developed bleeding during dabigatran treatment required shorter intensive care support compared with those on warfarin.[60] Management of bleeding events in patients receiving dabigatran is supportive.[61] Thrombin clotting time and

ecarin clotting time can be used to assess anticoagulation status but INR should not be used for this purpose.[62, 63] Activated and non-activated prothrombin complex concentrate and recombinant factor VIIa can be used to enhance haemostasis.[64-66] Low-dose FEIBA (Baxter AG, Vienna, Austria) has been reported to correct laboratory measures of anticoagulant effect in patients treated with dabigatran.[67] Idarucizumab, a humanized antibody fragment (Fab) has been developed as a specific antidote for dabigatran in patients with uncontrolled bleeding or requiring emergency intervention (see below).

Periprocedural management of dabigatran

A quarter of the RE-LY patients had undergone invasive procedures during 2 years of follow up, with the most common reasons being diagnostic and dental procedures and insertion of implantable devices. Periprocedural bleeding rates were similar in patients receiving either dabigatran dose or warfarin (3.8% with dabigatran 110 mg, 5.1% with dabigatran 150 mg and 4.6% with warfarin). No significant difference in bleeding rates was seen in participants treated by dabigatran or warfarin who required urgent surgery, although bleeding complications were more frequent in all groups (17.8% with dabigatran 110 mg, 17.7% with dabigatran 150 mg, and 21.6% with warfarin).

Dabigatran simplifies perioperative management of OAC due to its prompt offset and onset of action, short half-life, more predictable pharmacodynamic and pharmacokinetic characteristics and less drug interactions compared to warfarin. Consequently dabigatran allows a shorter interruption of OAC compared to warfarin

and thus shorter expose to increased risk of stroke.[68] The risk of major periprocedural bleeding with dabigatran as with any OAC depends on the type of procedure. Procedures with low risk of bleeding, such as gastric endoscopy, superficial skin surgery, including skin biopsies, minor dental procedures or wound revisions do not require interruption in dabigatran treatment. Minimal risk procedures should be performed at trough concentration, whilst avoiding the peak concentrations around 2 hours after ingestion.[69] Elective cardioversion is safe in subjects receiving dabigatran for 3 weeks prior the procedure and it should be given for at least 4 weeks post procedure (usually lifelong).[70, 71]

Minor elective procedures, such as pacemaker insertion, coronary and other transluminal interventions, pleural and peritoneal puncture, eye surgery, endoscopy, laparoscopy, organ biopsies and dental extraction are often performed after omitting dabigatran for 24 hours before the procedure.[72] It has been shown to be safe to continue dabigatran during cardiac ablation procedures although more data are needed in this regard.[73] However, a recent meta-analysis suggested that periprocedural risk of stroke or transient ischemic attacks could be higher with dabigatran compared to warfarin (odds ration [OR] 3.94, 95% CI 1.54-10.08).[74] More data are essential to draw robust conclusions in this regard.

Major procedures such as open abdominal, thoracic, brain, vascular, orthopedic or trauma surgery that are associated with high bleeding risk may require a longer dabigatran interruption.[72] Perioperative management of dabigatran does not usually require bridging therapy with heparin or low molecular weight heparin. However the balance of risks of stroke and bleeding needs to be considered on individual basis.

Dabigatran can be restarted as soon as effective hemostasis has been achieved after surgery. More prolonged interruption of dabigatran may be needed in patients with compromised kidney function, due to renal elimination of the drugs.[69] In patients receiving dabigatran major surgery should be postponed if possible to allow the drug elimination.[75] Dabigatran plasma levels can provide some help in estimation of periprocedural bleeding risk. Working Group on Perioperative Haemostasis (GIHP) proposed a cut-off concentration of 30 ng/ml, with surgery deemed safe with plasma levels below this threshold.[64]

Net clinical benefit

Clinical utility of dabigatran for stroke prevention in AF is supported by net clinical benefit analyses. In the population of the RE-LY trial both dabigatran doses decreased ischemic stroke equivalents: by 0.92 per 100 patient years (95% CI 1.74-0.21) with dabigatran 110 mg bid and by 1.08 (95% CI 1.86-0.34) with dabigatran 150 mg bid.[76]

At present no data are available on direct comparisons of net clinical benefits between different non-VKA OAC. However in a stepwise, fixed-effects meta-analysis of bid vs. once daily regimens in Phase III trials showed significant advantage of dabigatran 150 mg bid dose for stroke and systemic embolism prevention compared to once daily regimes used for rivaroxaban and edoxaban (HR 0.75, 95% CI 0.58-0.96).[77] One may speculate that the higher dabigatran dose could be considered a treatment of choice in patients with high risk of stroke, although direct evidence supporting the approach is to be obtained yet.

Real-World Evidence

Medicare FDA Data

Completion of the phase III clinical trials of dabigatran in non-valvular AF and its clinical approval was followed by assessment of efficacy and safety of dabigatran in settings of general practice. The Medicare FDA database that included information on 134, 414 AF patients was used to form a propensity score-matched cohort of elderly individuals (75 years and above) treated with dabigatran or warfarin.[78] The analysis showed that treatment with dabigatran was associated with lower rates of ischemic stroke (HR 0.80, 95% CI 0.67-0.96); intracranial hemorrhage (HR 0.34, 95% CI 0.26-0.46); and death (HR 0.86, 95% CI 0.77-0.96), but higher risk of major gastrointestinal bleeding (HR 1.28, 95% CI 1.14-1.44). These associations were most prominent in patients receiving the 150 mg dabigatran dose. Similar rates of myocardial infarction were noted with both treatments (HR 0.92, 95% CI 0.78-1.08). Of interest, the analysis included a significant proportion of patients treated with reduced 75 mg bid dabigatran dose despite the fact that most of those patients did not have severe renal impairment.[78] This likely reflects overall misperception of high risk of bleeding related to use of oral anticoagulation and temptation to reduce the perceived risk of bleeding by use of the lower dose of 75 mg bid of the drug despite the fact that they have never been tested in clinical trials.

Harvard Study

The Harvard group used US health care utilization data to assess incidence of stroke and bleeding events in patients newly started on warfarin or dabigatran. Groups of 2,991 users were formed for each drug using propensity score matching. The analysis

did not find significant difference in stroke (HR 1.05, 95% CI 0.64-1.70) or major bleeding (HR 0.97, 95% CI 0.69-1.36) between the two anticoagulants. The analysis is limited by relatively short follow up of 1,237 person-years with dabigatran and 950 person-years with warfarin.[79] A pooled analysis of two major US health insurance databases that included 19,189 propensity score matched dabigatran initiators indicated reduction in major hemorrhage in dabigatran users (HR 0.75, 95% CI 0.65-0.87 based) with a trend towards less strokes in these patients (HR 0.77, 95% CI 0.54-1.09). There was no heterogeneity of outcome in various patient subgroups, but the analysis is limited by the short duration of follow up (5 months for dabigatran and 4 months for warfarin) and small event numbers.[80]

Department of Defense analysis

The US Department of Defense Military Health System database provided information on 12,793 propensity matched patients for each dabigatran and warfarin with a longer follow up (average of 297 days in the dabigatran group and 215 days in the warfarin group). The dabigatran patients had a higher probability of event-free survival (adjusted HR 0.73, 95% CI 0.55-0.97 for strokes, HR 0.49, 95% CI 0.30-0.79 for major intracranial bleeding, HR 0.65, 95% CI 0.45-0.95 for myocardial infarction and HR 0.64, 95% CI 0.55–0.74 for death) with a non-significant trend towards higher rates of major bleeding.[81]

GLORIA-AF Registry

GLORIA-AF (Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation) is a large multinational registry program setup to establish factors that influence choice of stroke prevention strategies in patients with

non-valvular AF (CHA_2DS_2-VASc score ≥1). The program aims to enrol up to 56,000 patients in nearly 50 countries and it includes 3 phases: Phase I, before the introduction of novel OACs, Phase II, after the introduction of dabigatran into practice; and Phase III, analysis of large treatment groups, subjected for propensity score matching to account for demographic and clinical differences in real-world data.[82, 83]

In Phase I 1063 patients were enrolled, 67.1% in Asia, 27.4% in Europe and 5.6% in Middle East. The analysis showed noticeable regional differences in utilization of oral anticoagulation. For example, the majority of patients in China received antiplatelet agents (53.7%) with about 2-fold lower rates of aspirin utilization in other regions. In contrast, in the EU almost 64% of patients were treated with VKAs. VKAs were used in about 30% of Middle East patients.[84] Initial Phase II data emerged from North America where dabigatran had earlier approval for clinical use. In 1672 North American AF patients 76.4% received oral anticoagulation (including dabigatran in 32.1% and VKA in 29.2%), whilst almost half of patients in China had no or inadequate antithrombotic therapy. Overall, patients started on dabigatran and VKAs had similar baseline stroke and bleeding risk, but patients prescribed dabigatran were older and included more subjects with kidney dysfunction, diabetes, and congestive heart failure.[85] Further data from the GLORIA program are awaited with interest.

Danish Registry

Propensity matched analysis of the Danish Registry of Medicinal Product Statistics involving 4978 patients receiving dabigatran and 8936 patients treated with warfarin showed similar rates of stroke and systemic embolism with the two treatments.

However treatment with dabigatran was associated with lower mortality (adjusted HR 0.79, 95% CI 0.65-0.95 for 110 mg dose and adjusted HR 0.57, 95% CI 0.40-0.80 for 150 mg dose). Patients receiving either dose of dabigatran were also at lower risk of pulmonary embolism, intracranial bleeding, and myocardial infarction. Furthermore, use of 110 mg dose of dabigatran was associated with lower risk of gastrointestinal bleeding compared to warfarin. These data indicate that in everyday practice dabigatran could bring more clinical benefits compared to warfarin than it could be expected based on clinical trials, perhaps do to suboptimal INR control in some patients receiving warfarin.[86]

Real world data confirm efficacy and safety of dabigatran in older people

In a population-level analysis from the North America, based on a cohort of 15,918 AF patients on dabigatran and 47,192 matched patients receiving warfarin 67% of patients were 75 years or older.[58] In the elderly group dabigatran showed the same effectiveness for stroke prevention as warfarin (HR 1.05, 95% CI 0.93-1.19) for both dabigatran doses, but dabigatran was linked with less intracranial bleeding (HR 0.60, 95% CI 0.47-0.76) and more gastrointestinal hemorrhages (HR 1.30 95% CI 1.14-1.50). The 2014 UK NICE guidelines on AF list 110 mg dabigatran dose as an alternative to warfarin in people 75 years or older.[87]

Mechanical heart valves

Despite its remarkable success in revolutionising oral anticoagulation in non-valvular AF and VTE management, dabigatran was not successful in the management of some prothrombotic conditions. The phase 2 randomised RE-ALIGN trial tested the utility of the drug started 4-7 days after mechanical aortic- or mitral-valve replacement, or in

patients who had undergone mechanical valve replacement at least three months earlier.[88] Dabigatran was started at 150, 220 or 300 mg bd dose depending on renal function and further corrected to maintain trough plasma level of 50 ng/mL or higher. Warfarin served as a comparator. The study was terminated early due to increased rates of thromboembolic and bleeding complications in the dabigatran arm. The results likely reflect inability of the drug to block coagulation activation stimulated by exposure of the blood to mechanical heart valves, particularly in the early post-operative period when blood levels of the drug were lower.

Outlook

New Studies

Several new studies aim to complete important gaps in knowledge on possible utility of dabigatran. Embolic strokes of undetermined source (a subgroup of cryptogenic strokes) represent 20-25% of all ischemic strokes and often related to 'silent' AF. The ongoing RESPECT-ESUS study is an phase III, double-blind, randomized clinical trial that compares 150 mg bid or 110 mg bid dabigatran with 100 mg once daily aspirin for secondary stroke prevention in patients with embolic stroke of undetermined source in 6000 patients over observation period of 0.5-3 years.[89]

The RE-CIRCUIT (Randomized Evaluation of dabigatran etexilate Compared to warfarin in pulmonary vein ablation: assessment of an uninterrupted periprocedural anticoagulation strategy) trial aims to determine utility of dabigatran (150 mg bid) treatment during cardiac ablation procedures compared with warfarin in over 700

patients with paroxysmal or persistent AF. The study will compliment available observational studies, and meta-analyses.[90]

The RE-DUAL PCI (Randomized Evaluation of Dual Therapy with Dabigatran vs. Triple Therapy Strategy with Warfarin in Patients with NVAF that have undergone PCI with Stenting) non-inferiority trial compares combination of dabigatran (110 mg bid or 150 mg bid) plus clopidogrel or ticagrelor with a triple antithrombotic therapy of warfarin plus clopidogrel or ticagrelor plus aspirin in patients AF undergoing percutaneous coronary intervention.

A further phase IV study is expected to assess dabigatran for the treatment of VTE in the real world.[91] RE-COVERY is a prospective cohort non-interventional study of dabigatran for the management of VTE. The study is aimed to characterize patients with DVT or PE, to evaluate therapeutic strategies, and to assess the safety and effectiveness of dabigatran versus VKAs in routine care.[92]

Idarucizumab

Dabigatran has a favorable predictable pharmacokinetic profile with reasonably low risk of bleeding complications. However a number of clinical situations would still require prompt reversal of the drug activity. Those situations could be related to serious and life-threatening bleeding events (e.g. intracerebral bleeding), cases of drug overdose and emergency surgery.

A specific humanized Fab, idarucizumab, was developed as a reversal agent for dabigatran. The antibody binds dabigatran with high affinity and prevents inhibition

of thrombin by dabigatran. Idarucizumab was initially tested in pig blunt liver trauma model where animals not receiving idarucizumab consistently died from bleeding.[93] Treatment with idarucizumab led to dose-dependent reduction in blood loss with only 17% mortality and 50% reduction in blood loss seen even with the lowest tested idarucizumab dose (30 mg/kg). Higher, 60 or 120 mg/kg idarucizumab doses were associated with 100% survival of the treated animals.

In a randomized, double-blind, placebo controlled study of 145 healthy volunteers all tested doses of idarucizumab (up to 8 g) were well tolerated and safe and the agent provided immediate, complete and sustained reversal of dabigatran induced anticoagulation.[94] It has been further shown that 5 g of idarucizumab provides fast complete reversal of dabigatran induced anticoagulation in mid-aged and elderly healthy individuals and patients with kidney dysfunction.[95] Moreover, further oral intake of dabigatran 24 hours after administration of idarucizumab restored adequate anticoagulation. In all available reports idarucizumab was well tolerated and its availability would provide further confidence for clinicians and safety for patients. [96]

An analysis of the first 90 patients enrolled in the ongoing, multicenter, prospective cohort Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD) trial included 51 patients with overt, uncontrollable, or life-threatening bleeding (mostly intracranial or gastrointestinal hemorrhage) and 39 patients in need for emergency invasive procedures, which required normal hemostasis.[97] Over 90% of the participants were treated with dabigatran for stroke prevention in view of AF. The primary end point was reversal of the anticoagulant effect of dabigatran within 4

hours of completion of the drug infusion as tested by the dilute thrombin time or ecarin clotting time. Intravenous administration of 5 g of idarucizumab rapidly and completely reversed the anticoagulant effect of dabigatran in 88-98% of the patients with prolonged clotting times. In patients who underwent an intervention, normal hemostasis was achieved in 92% with mild-to-moderate hemostasis impairment reported in 8%. There were 5 thrombotic events recorded at the time of the analysis, all of which occurred off anticoagulants. Idarucizumab has been approved in the US for uncontrollable or life-threatening bleeding and/or in need for emergency invasive procedures of surgery.[98] Approval of the agent in the EU was also granted.[99]

Overall perspectives

In view of significant pharmacokinetic and pharmacodynamic limitations of warfarin introduction of non-VKA oral anticoagulants was awaited with great interest. With growing evidence of efficacy and safety of dabigatran for several indications, together with its ease of use and expected to reduce costs, the drug along with other non-VKA oral anticoagulants are becoming the first-line option for most indications for oral anticoagulation. Until further development warfarin will remain the treatment of choice for patients with advanced renal disease and management of mechanical prosthetic valves. Currently, there are no robust data to suggest the superiority of one non-VKA oral anticoagulant over another. However, dabigatran benefits from the longest record of clinical use and the availability of a specific reversal agent.

Conclusion

Dabigatran is an oral direct thrombin inhibitor that can be used with fixed doses and no need for routine monitoring. The drug benefits from few inter-drug interactions. Dabigatran is effective for the prevention of stroke and systemic thromboembolism in AF and for management of VTE. The agent has excellent safety profile with no evidence of liver toxicity and clear reduction in intracranial hemorrhage risk compared to warfarin. A specific reversal agent for dabigatran has been approved by FDA in the US, Committee for Medicinal Products for Human use (CHMP) of the European Medicines Agency (EMA) in the EU and Health Canada in Canada.

Conflict of interest

GYHL: Guideline membership/reviewing: ESC Guidelines on Atrial Fibrillation, 2010 and =Chairman, Scientific Documents Committee, European Heart Rhythm Association (EHRA). Reviewer for various guidelines and position statements from ESC, EHRA, NICE etc. Steering Committees/trials: Includes steering committees for various Phase II and III studies, Health Economics & Outcomes Research, etc. Investigator in various clinical trials in cardiovascular disease, including those on antithrombotic therapies in atrial fibrillation, acute coronary syndrome, lipids, etc. Consultant for Bayer/Jensen J&J, Astellas, Merck, Sanofi, BMS/Pfizer, Biotronik, Medtronic, Portola, Boehringer Ingelheim, Microlife and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche and Daiichi-Sankyo

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Table 1. Pharmacological characteristics

	Dabigatran	Warfarin
Target	Factor II (thrombin)	Vitamin K dependent factors: II, VII, IX and X
Bioavailability	6.5%	>95%
Peak concentrations	1-2 h	0.3 to 4 h
Half life	14-17 h	35-45 h
Protein binding	35%	>98%
Renal excretion	80%	0%
Potential interactions	P-gp inhibitors, potent P-gp inducers	Inhibitors of CYP2C9, 3A4, 1A2

Table 2. Randomized clinical trials of dabigatran in major joint surgery

	Duration of treatment	Initiation of dabigatran post operation	VTE and all-cause mortality (%)		
			Dabigatran 150 mg od	Dabigatran 220 mg od	Enoxaparin
Total heap replacement					
RE-NOVATE (n=3494)	6-10 days	1-4 h (with half dose)	6.7	8.6	6.0†
Total knee replacement					
RE-MODEL (n=2076)	6-10 days	1-4 h (with half dose)	37.7	40.5	36.4†
RE-MOBILIZE (n=1896)	12-15 days	6-12 hours post operation	25.3*	33.7*	31.1‡

*Inferior to enoxaparin, †40 mg s.c. once daily, ‡ 30 mg s.c. twice daily. od, once daily.

Table 3. Randomized clinical trials of dabigatran 150 mg bid in venous thromboembolism

Study	Number	Comparator Treatment	Recurrent VTE HR (95% CI)	All death HR (95% CI)	Major bleeding HR (95% CI)	Any bleeding HR (95% CI)
Long-term treatment of acute VTE						
RE-COVER [39]	2539	Warfarin	1.10 (0.65-1.84)	0.98 (0.53-1.79)	0.82 (0.45-1.48)	0.71 (0.59-0.85)*
RE-COVER II[40]	2589	Warfarin	1.08 (0.64-1.80)	0.98 (0.56-1.71)	0.69 (0.36-1.32)	0.67 (0.56-0.81)‡
Pooled RE-COVER and RE-COVERII[40]	2539+2589	Warfarin	1.09 (0.76-1.57)	1.0 (0.67-1.51)	0.73 (0.48-1.11)	0.70 (0.61-0.79)‡
Extended treatment for prevention of VTE recurrence						
RE-MEDY[53]	2856	Warfarin	1.44 (0.78-2.64)	0.90 (0.47-1.72)	0.52 (0.27-1.02)	0.71 (0.61-0.83)*
RE-SONATE[53]	1343	Placebo	0.08 (0.02-0.25)*		Not estimable	1.82 (1.23-2.68)†

*p<0.001; †p≤0.01; ‡p<0.05; bid, twice daily; CI, confidence interval; HR, hazard ratio; VTE, venous thromboembolism;

RE-COVER and RE-COVER II - treatment for 6 months, with prior intravenous heparin or subcutaneous low molecular weight heparin for a median of 9 days. RE-MEDY- treatment for median of 16 months (6 to 36 months) with prior anticoagulation at least for 3 months.

RE-SONATE – treatment for 6 months with prior anticoagulation at least for 3 months.

Figures legends:

Figure 1. Substudies of the RE-LY trial on effectiveness of dabigatran 110 mg vs warfarin for prevention of stroke and systemic embolism

*Results for VKA, previous stroke/TIA, cardioversion and patients from Japan presented as relative risk (95% CI); bid, twice daily; CI, confidence interval; INR, international normalised ratio; TIA, transient ischaemic attack; TTR, time in therapeutic range; VKA, Vitamin K antagonist. Eikelboom et al. (2011)[25]; Nagarakanti et al. (2013) [100]; Ferreira et al. (2013)[101]; Hijazi et al. (2014)[24]; Oldgren et al. (2011)[26]; Dans et al. (2013)[102]; Hori et al. (2013)[103]; Ezekowitz et al. (2010)[104]; Wallentin et al. (2010)[105]; Diener et al. (2010)[106]; Nagarakanti et al. (2011)[70]; Hori et al. (2011)[107].

Figure 2. Substudies of the RE-LY trial on effectiveness of dabigatran 150 mg vs warfarin for stroke and systemic embolism prevention

*Results for VKA, previous stroke/TIA, cardioversion and patients from Japan presented as relative risk (95% CI); bid, twice daily; CI, confidence interval; INR, international normalised ratio; TIA, transient ischaemic attack; TTR, time in therapeutic range; VKA, Vitamin K antagonist. Eikelboom et al. (2011)[25]; Nagarakanti et al. (2013) [100]; Ferreira et al. (2013)[101]; Hijazi et al. (2014)[24]; Oldgren et al. (2011)[26]; Dans et al. (2013)[102]; Hori et al. (2013)[103]; Ezekowitz et al. (2010)[104]; Wallentin et al. (2010)[105]; Diener et al. (2010)[106]; Nagarakanti et al. (2011)[70]; Hori et al. (2011)[107].

Figure 3. Substudies of the RE-LY trial on risk of major bleeding with dabigatran 110 mg vs warfarin

*Results for VKA, periprocedure bleeding, previous stroke/TIA, cardioversion and patients from Japan presented as relative risk (95% CI) bid, twice daily; CI, confidence interval; INR, international

normalised ratio; TIA, transient ischaemic attack; TTR, time in therapeutic range; VKA, Vitamin K antagonist. Eikelboom et al. (2011)[25]; Nagarakanti et al. (2013) [100]; Ferreira et al. (2013)[101]; Hijazi et al. (2014)[24]; Oldgren et al. (2011)[26]; Dans et al. (2013)[102]; Hori et al. (2013)[103]; Ezekowitz et al. (2010)[104]; Wallentin et al. (2010)[105]; Healey et al. (2012)[68]; Diener et al. (2010)[106]; Nagarakanti et al. (2011)[70]; Hori et al. (2011)[107].

Figure 4. Substudies of the RE-LY trial on safety of dabigatran 150 mg vs warfarin on risk of major bleeding

*Results for VKA, periprocedure bleeding, previous stroke/TIA, cardioversion and patients from Japan presented as relative risk (95% CI) bid, twice daily; CI, confidence interval; INR, international normalised ratio; TIA, transient ischaemic attack; TTR, time in therapeutic range; VKA, Vitamin K antagonist. Eikelboom et al. (2011)[25]; Nagarakanti et al. (2013) [100]; Ferreira et al. (2013)[101]; Hijazi et al. (2014)[24]; Oldgren et al. (2011)[26]; Dans et al. (2013)[102]; Hori et al. (2013)[103]; Ezekowitz et al. (2010)[104]; Wallentin et al. (2010)[105]; Healey et al. (2012)[68]; Diener et al. (2010)[106]; Nagarakanti et al. (2011)[70]; Hori et al. (2011)[107]

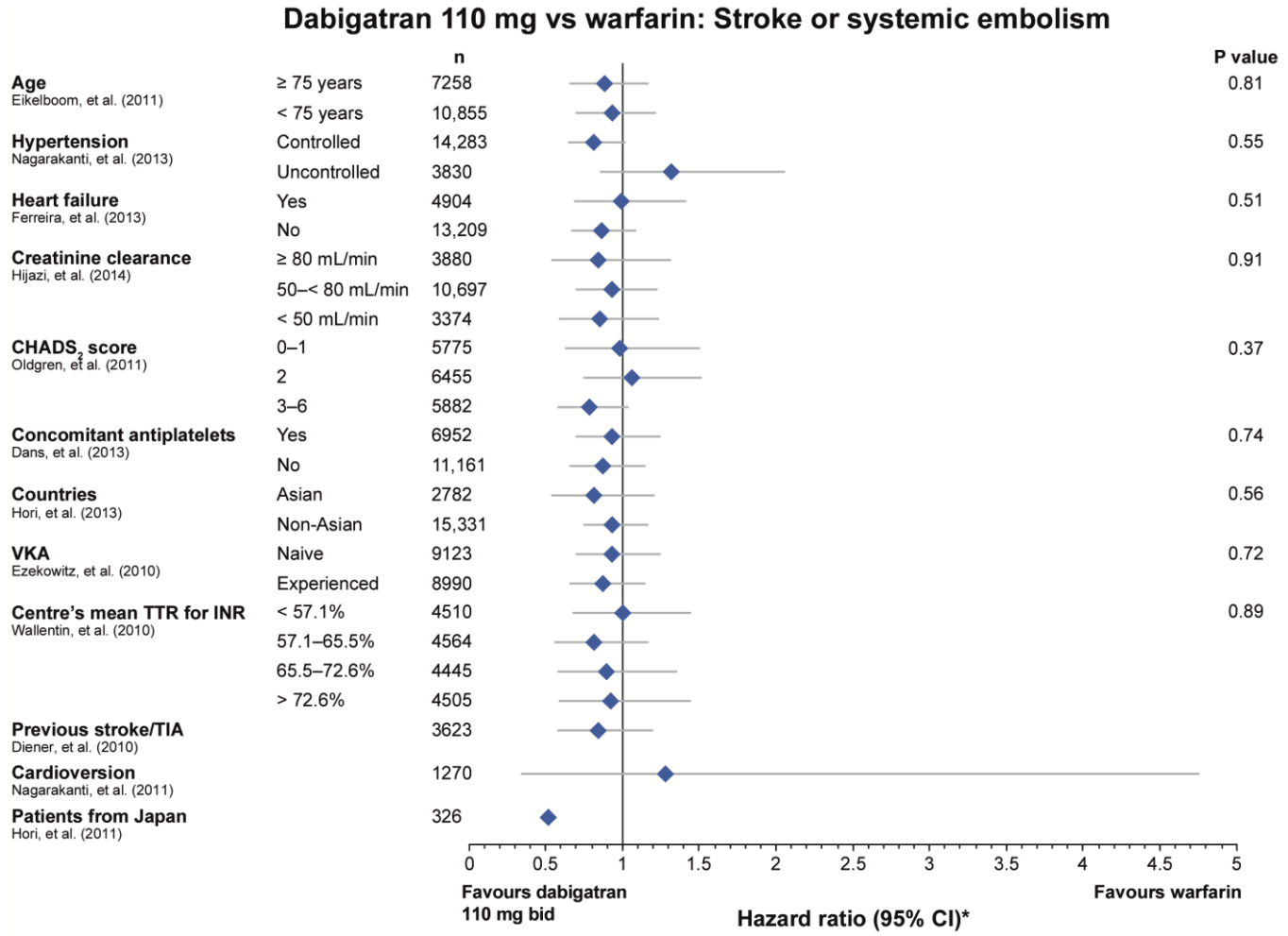

Figure 1

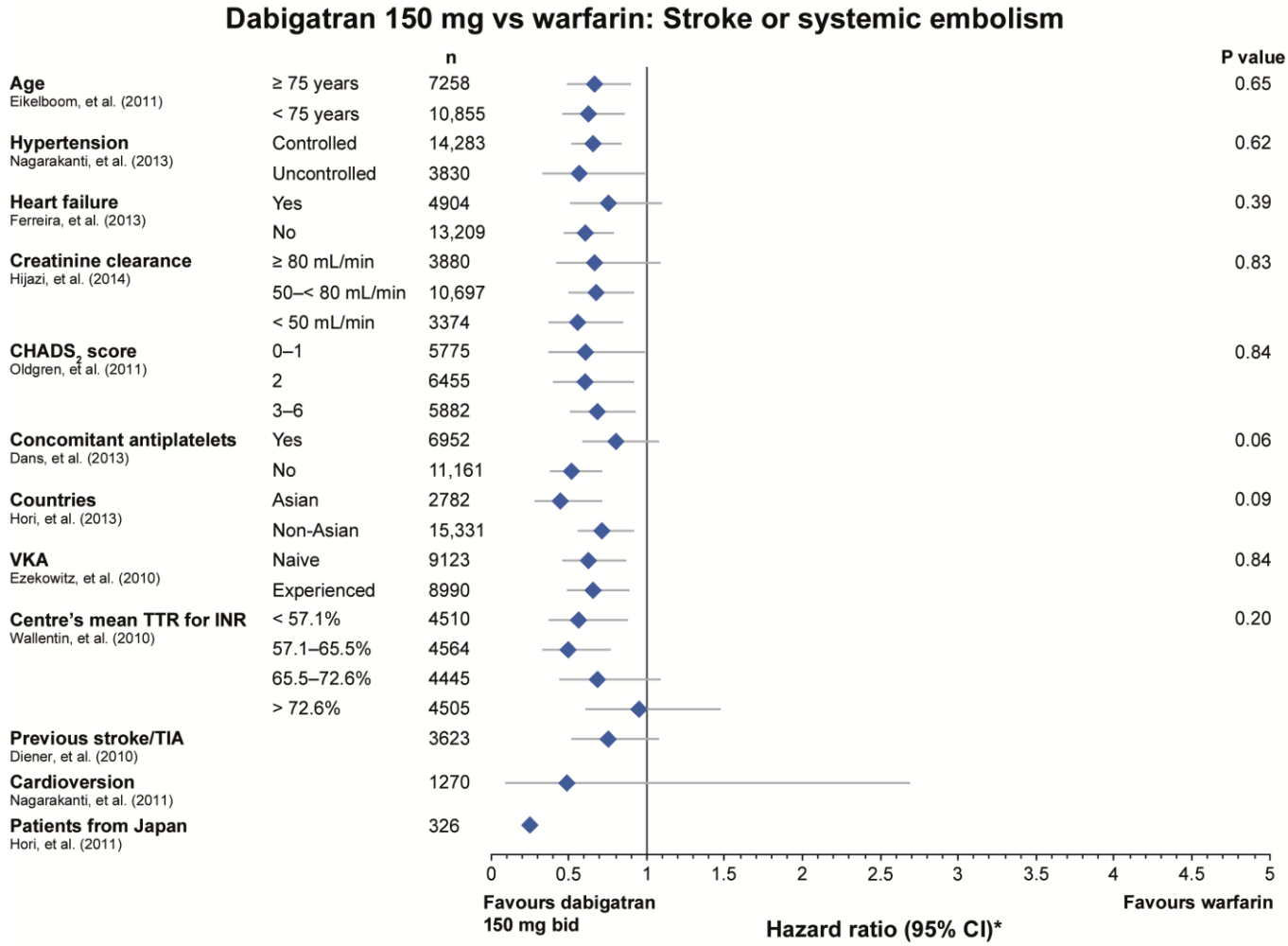

Figure 2

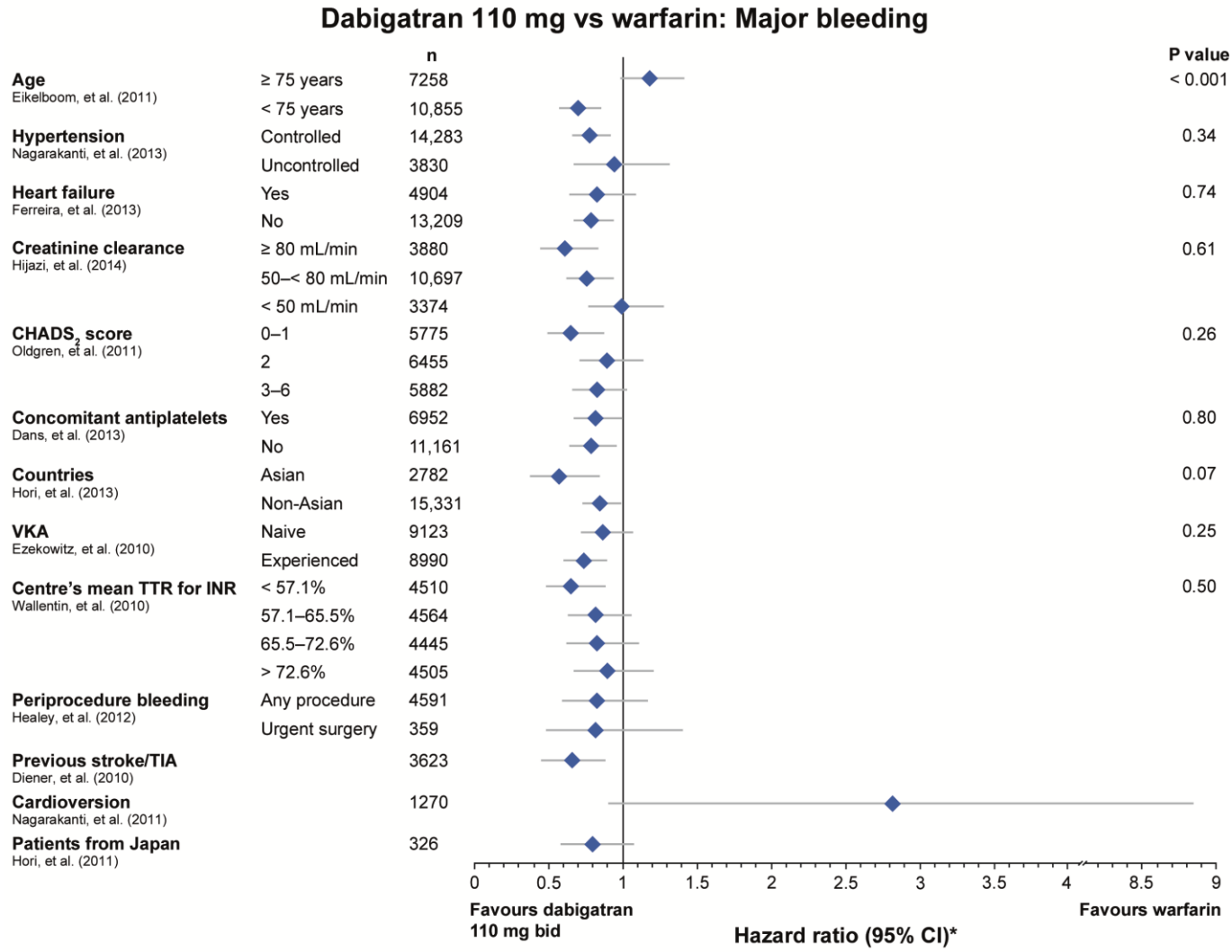

Figure 3

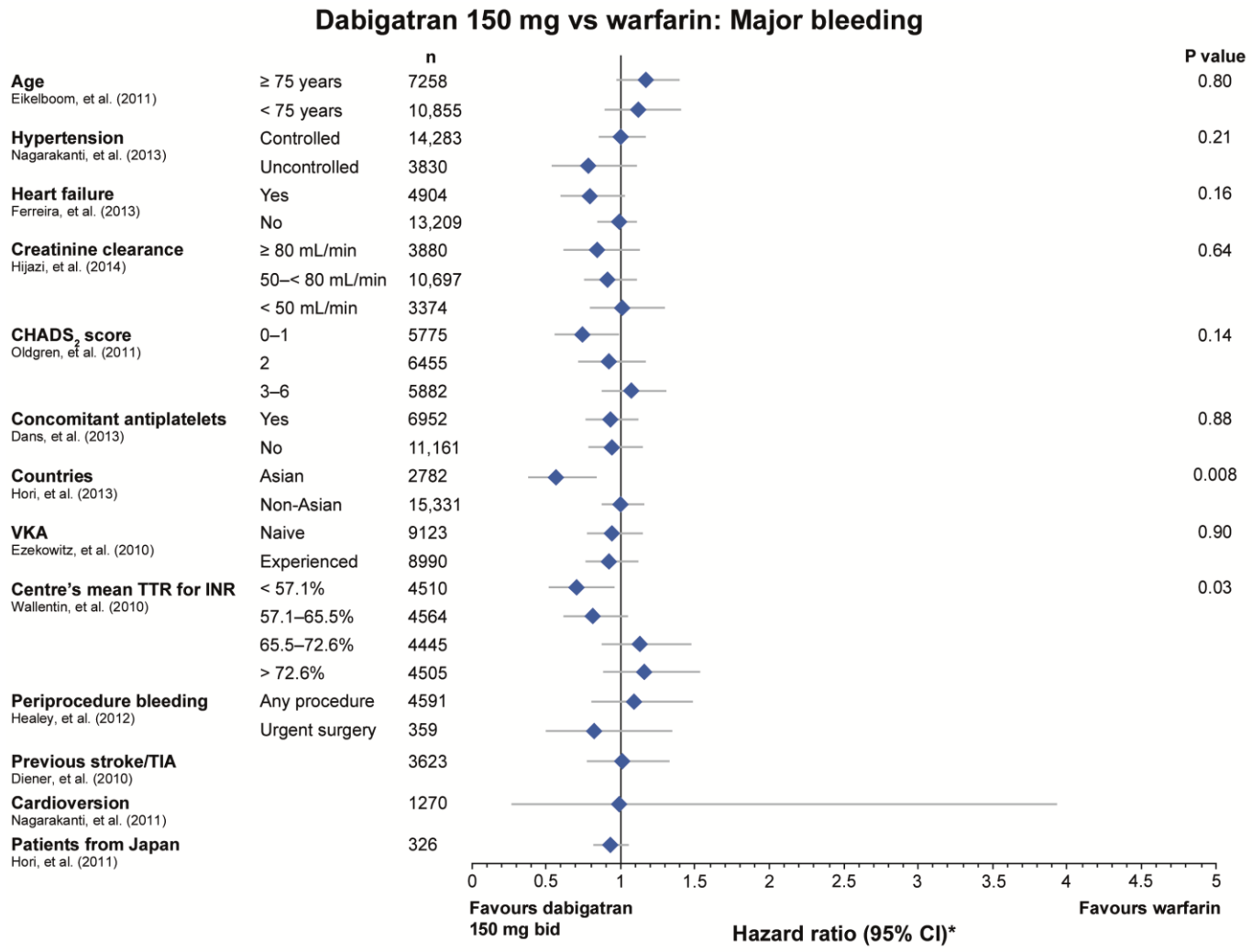

Figure 4

Highlights

- Dabigatran is a direct thrombin inhibitor used with fixed doses.
- The drug is effective for stroke prevention in atrial fibrillation.
- Dabigatran used for the management of venous thromboembolism.
- Dabigatran shows a reduction in intracranial haemorrhage risk compared to warfarin.
- A specific reversal agent for dabigatran has been approved by FDA and EU.